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PARA-AMINO BENZOIC ACID IN THE TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER*†

A Report of Its Use in 17 Cases

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The use of para-amino benzoic acid (PABA) in the treatment of rickettsial diseases has been discussed in several recent reports. The first clinical investigation, reported by Yeomans et al.[1] in 1944, demonstrated that a favorable therapeutic effect could be obtained in louse borne typhus with PABA. These authors emphasized that early initiation of treatment was of singular importance in obtaining optimal results. Tierney[2] reported that PABA exerted a beneficial effect on the course of Tsutsugamushi disease in a series of 13 treated cases. Smith[3] managed 29 cases of murine typhus with PABA and concluded that patients receiving PABA progressed more favorably and followed a more benign course than those untreated.

Rose et al.[4] reported the first instance of the use of PABA in Rocky Mountain spotted fever. They treated one case with apparently beneficial results. Since then several other reports [5, 6, 7, 8, 9] have appeared which indicate that PABA decreases both the morbidity and mortality of Rocky Mountain spotted fever in children and adults.

In a previous paper[10] we reported the use of PABA in 8 cases of spotted fever during the summer of 1946 at Children's Hospital, Washington, D. C. It was demonstrated that PABA exerted a beneficial effect on the course of the disease. The present report gives the results in the treatment of nine additional cases of Rocky Mountain spotted fever in the summer of 1947. In view of the relatively small number in the total group it was not possible to run a control series of untreated cases. However, the PABA treated patients may be compared to previous experiences with Rocky Mountain spotted fever prior to the advent of PABA. Ong and Raffeto[10a] have reported on 18 cases managed at Children's Hospital up to 1940.

MANAGEMENT OF CASES

a. *Laboratory.* A standard procedure was adopted for all cases under treatment during 1947 and consisted of the following:

* During the summer of 1948, several cases of spotted fever were treated with Aureomycin, a new antibiotic, with excellent results. These cases will be reported in a subsequent paper.

† This article appeared in the August 1948 issue of Pediatrics and is reprinted with the special permission of Dr. Hugh McCulloch.

1. Daily white and differential cell counts
2. Daily PABA levels (obtained one hour before the next dose)
3. Urinalysis every second day
4. NPN every second day
5. Cephalin flocculation test, prothrombin time, CO_2 combining power and total protein determinations before PABA therapy was started and every third day thereafter.
6. Weil-Felix and complement fixation tests as indicated for diagnosis (usually positive between 10–14 days after onset of the disease)
7. Fluid intake-output charts on all patients.

This daily evaluation of the patient is considered a requisite for optimal management.

b. *Specific Therapy.* In all cases, powdered PABA was dissolved in 5% bicarbonate solution so that 15 cc. of the mixture contained one gram of PABA.* This preliminary neutralization was designed to lessen gastric irritation. The mixture was chilled and given in fruit juice. During the first one or two days an occasional child was disinclined to take the medication orally. However, after toxicity subsided (usually within 24 to 48 hours), the patients took the drug readily and little vomiting was encountered. Yeomans et al.[1] reports one instance of tracheitis produced by aspiration of PABA. In the infrequent instance where a child is comatose, uncooperative or vomiting unduly, the drug may be gavaged or given parenterally. A 25 per cent solution of the sodium salt in a solution of sodium chloride is available for intravenous or intramuscular use. The oral route of administration is to be preferred. The dosage in this series ranged between 0.3 to 0.5 gram of PABA per pound of body weight in 24 hours using a 2 hour divided dosage schedule. Thus a 50 pound child received 15 to 25 gms. of the drug daily or 1.3 to 2 gms. every 2 hours throughout the day and night.

c. *Supportive Therapy.* The majority of patients in this series received supportive intravenous infusions including blood, plasma, crystalloids and protein hydrolysates intravenously to combat peripheral shock, dehydration and hypoproteinemia. In this regard, we are in complete agreement with Harrell et al.[11] that no deleterious effects followed intravenous alimentation in spotted fever as was formerly believed. A high carbohydrate, high protein diet with adequate vitamin supplements was routinely employed. Penicillin was used in 3 cases where a complicating bronchopneumonia appeared. Sulfonamides are definitely contraindicated in view of the demonstrated antagonism between sulfonamides and PABA as well as the untoward effect following the use of sulfonamides per se in rickettsial

* Several of the pharmaceutical firms are now putting up tablets of sodium PABA containing 0.5 gm.

infections. One patient who had myocarditis and congestive failure as an attendant complication was digitalized.

RESULTS

In 17 cases of Rocky Mountain spotted fever treated with PABA during the summers of 1946 and 1947, there were no deaths (Chart 1). This is to be compared with 30 cases of spotted fever managed at Children's Hospital between 1931 to 1945 inclusive who did not receive PABA in which there were 3 deaths (10%). This difference in mortality rate in the two groups is not statistically significant. However, a compilation of the results of treatment of spotted fever with PABA reported thus far, in addition to our own cases, lends itself more readily to statistical analysis regarding the efficacy of the drug (Chart 2). A total of 51 patients including 43 children and 8 adults have been reported on to date. Of this number, 48 (or 94.1%) recovered. Woodward[8] reported a death in a 2 year old child who was started on PABA on the 19th day. A second death was reported by Peterson et al.[12] in a child with fulminating spotted fever who received PABA starting on the fifth day; the child died shortly after entry into the hospital. The third fatality discussed by Flinn et al.[6] was that of a 67 year old man whose treatment was started on the eighth day. The NPN rose to 60 mgm. % and the patient died in uremia. At autopsy, he was found to have long-standing renal disease antedating the spotted fever. This over-all mortality rate of 5.9% is in contrast to the 25% mortality rate which has prevailed in the eastern type of spotted fever prior to the use of PABA.

There was a noticeable difference in the course of the disease in the treated and untreated cases of this series. A comparison of the temperature curves in both groups is shown in Chart 3. The points on the curves indicate the averages of the *highest* daily temperature for all cases in each group. As will be noted, there was a more rapid defervescence of temperature in the cases treated with PABA when compared with untreated patients. It should be pointed out that the response to PABA was more gradual than precipitous, and was not comparable to the dramatic response of susceptible infections to sulfonamides and antibiotic drugs. The secondary rise in average temperatures of the treated group from the 5th to the 8th day noted in Chart 3, is a reflection of the high febrile courses of cases #5 and #6 who developed a complicating pneumonitis and parotitis, and case #16 who was severely ill with associated myocarditis and pneumonitis. In the remaining 14 uncomplicated cases, the temperature came down to normal on an average of $5\frac{1}{2}$ days after the initiation of PABA therapy.

Similarly, it was our impression that the morbidity, and degree of toxicity was decreased in the cases treated with PABA. Usually by the second or

third day after initiation of the drug, the patients were no longer lethargic or hyper-irritable and the characteristic toxic appearance showed definite evidence of subsiding. The rash usually disappeared by the 5th to the 8th day in the patients receiving PABA.

The drug was administered for an average of 6 days and was usually discontinued within two to four days after the temperature returned to normal.

CHART 1

Summary of 17 Patients with Rocky Mountain Spotted Fever Treated with Para-Aminobenzoic Acid

CASE	AGE	WEIGHT	DAY OF DISEASE PABA STARTED	DAYS OF FEVER AFTER PABA STARTED	DURATION OF PABA	MAXIMUM PABA LEVEL	TOTAL PABA	LOWEST WBC	HIGHEST CEPH. FLOCCULATION	LOWEST PROTHROMBIN	LOWEST TOTAL PROTEIN	SEVERITY OF CASE	OUTCOME	PABA
	years	*lbs.*			*days*	*mgms. %*	*gms.*			*%*				*gms./lb./24°*
M. Z.	7½	56	4	4	4	67	104	6000	4+	95	5.9	2+	Recovery	0.5
M. L.	9	66	4	4	4	80	114	4400	4+	61	4.62	3+	Recovery	0.5
L. H.	3	32	4	4	4	3	62	4200	4+	87	6.69	3+	Recovery	0.5
M. B.	2½	24	4	3	6	13.3	64	4900	4+	80	6.6	1+	Recovery	0.5
R. R.	7	40	3	2	3	66.6	32	3700	2+	100	4.9	2+	Recovery	0.6
E. H.	8	40	4	2	4	53	58	5100	2+	95	6.56	1+	Recovery	0.5
F. W.	5	30	7	3	6	25	59	3400	3+	80	4.83	3+	Recovery	0.3–0.4
M. J. P.	5	28	7	4	6	44	84	3600	3+	62	4.12	3+	Recovery	0.3–0.4
B. P.	7	47	11	16	5	100	110	7100	4+	87	4.21	4+	Recovery	0.25–0.70
D. B.	4	37	9	6	10	24	108	3600	4+	50		2+	Recovery	0.3
S. H.	7	45	9	5	10	37	202	6100			5.8	2+	Recovery	0.5
D. V.	1½	19	2	2	8	40	74	5700	3+	70	6.5	1+	Recovery	0.6
S. W.	8	50	10	12	9	35	186	9500	4+		5.7	3+	Recovery	0.5
J. M.	4	31	8	22	4	80	36	8500	4+		4.7	4+	Recovery	0.25
C. C.	11	82	8	11	9	40	104	4700	4+		3.9	4+	Recovery	0.2–0.3
C. L.	26	150	10	4	6	27	162	7100			7.1	3+	Recovery	0.2
R. L.	26	150	6	3	7	29	132	6100			7.2	2+	Recovery	0.2

CORRELATION BETWEEN TIME OF INITIATION OF PABA AND RESPONSE TO THERAPY

Of the 10 cases treated with PABA on or *before* the 7th day of the disease, none showed temperature beyond four days after initiation of therapy; the average for this group was three days. Of the remaining seven cases started on PABA therapy *after* the seventh day, the average duration of fever following initiation of PABA was 10 days. Of the three patients who

ran a severe course and developed complicating pneumonitis, two (cases #5 and #6) were started on the 8th day while the third (case #16) received the first dose of PABA on the 16th day.

CHART 2

Compilation of the Results of Treatment of Spotted Fever with Paba Reported thus Far

AUTHOR	NUMBER OF PATIENTS	NUMBER OF RECOVERIES	% RECOVERIES
Rose et al.[4]	1	1	100
Flinn et al.[6]	10	9	90
Ravenel[7]	5	5	100
Maroney et al.[5]	1	1	100
Woodward[8]	13	12	92.3
Hendricks et al.[9]	1	1	100
Peterson et al.[12]	3	2	66.6
Children's Hospital, Washington, D. C.	17	17	100
	51	48	94.1%

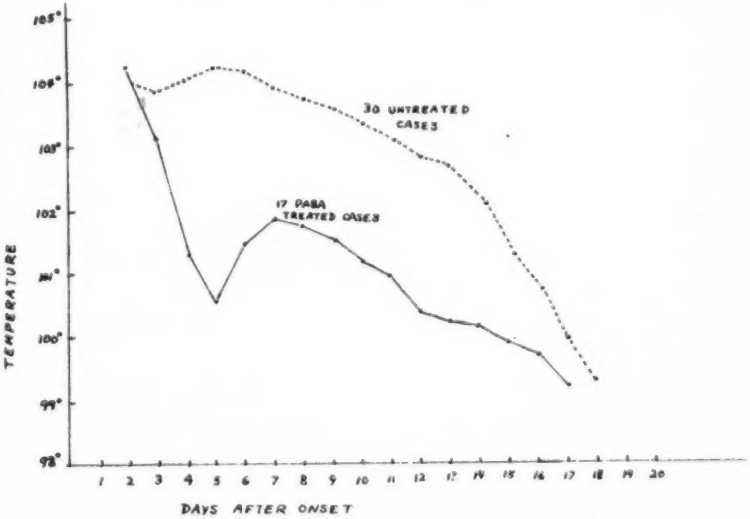

CHART 3. A comparison of the temperature curves in the treated and untreated series of cases of spotted fever. The points on the curves indicate the averages of the highest daily.

There appears to be little doubt both from the reports of others[1, 2, 13] as well as our own observations that the earlier the initiation of PABA

therapy, the better the response (Chart 4). Favorable therapeutic results can probably be expected if the drug is started before the seventh day; however, the optimal time for initiating treatment probably lies between two to four days after the onset of the disease. This is predicated by the fact that rickettsia reside and multiple intracellularly largely within the endothelial cells of small vessels. PABA must theoretically gain access to the organisms located within the cells where it inhibits the intracellular multiplication of the rickettsia. Unfortunately, early hospitalization in cases of Rocky Mountain spotted fever is the exception rather than the

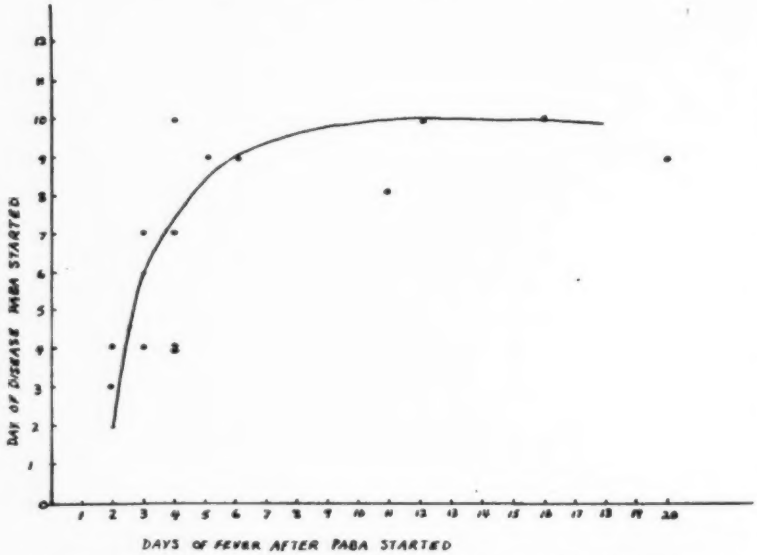

CHART 4. Correlation between the time of initiation of PABA therapy and the duration of fever.

rule. Only five of our 17 cases were started on PABA before the fifth day. This emphasizes the need for early detection of the disease, possibly even before the appearance of the rash. A recapitulation of the early preeruptive symptoms would include high fever (ranging between 102–104°), malaise, headache, aching extremities, anorexia and chilly sensations which in themselves are rather nonspecific and would be unlikely to allow a diagnosis of spotted fever without a history of tick bite. The latter is often not elicited. The appearance of the rash which is usually on the third or fourth day after the onset of fever usually permits the diagnosis to be made readily. From present data it would seem that if PABA was begun at this

time, the efficacy of the drug would be enhanced. In areas where there is an unusual geographic concentration of spotted fever the physician should be on the alert for the occurrence of the disease during the summer months. All patients in such areas should be routinely questioned for history of tick bite in instances of cryptogenic fever.

SCHEDULE OF DOSAGE

The optimal dose of PABA in spotted fever requires further clarification both in children and adults. In a previous communication,[10] we reported that 0.33 to 0.5 gm. per pound of body weight per 24 hours in a 2 hour di-

CHART 5

Average Blood Level of PABA Correlated with the Dosage in 15 Cases in Children
Note the variation in the blood levels obtained with comparable dosage

CASE NO.	WEIGHT OF PATIENT	DOSE/LB./24 HR.	AVERAGE PABA BLOOD LEVEL
		gms.	*mgm. %*
1	37	0.3	20
2	45	0.5	29
3	19	0.6	33
4	50	0.5	19
5	31	0.25	53
6	82	0.25	20
9	50	0.5	49
10	66	0.5	36
11	32	0.5	3
12	24	0.5	8
13	40	0.6	66
14	40	0.5	32
15	30	0.35	10
16	28	0.35	22
17	47	0.4	62

vided dosage schedule for children would usually yield a PABA blood level ranging between 15 to 40 mgm. %. This has been more or less substantiated by the findings in our more recent cases. In the two groups consisting of fifteen children ranging in weight from 20 to 80 pounds, seventy-one PABA assays were performed during the course of therapy (an average of five per patient). There was considerable variation in the blood level achieved with comparable dosage; no definite linear or curvilinear correlation between dosage and blood concentration was noted (Chart 5). For example in two cases (# 11 and # 12) the average blood level was 3 mgm. % and 8 mgm. % respectively in spite of a dose of 0.5 gm. per pound in 24 hours. The variation in the anticipated PABA blood levels with a given

dose of the drug may be explained either by the differential rate of excretion of the drug or a different rate of metabolism. It is pertinent to point out that the drug is excreted very rapidly in the urine and at the end of two to three hours, only minimal amounts are still present in the blood. In view of the variability of fluid intake and output in children with Rocky Mountain spotted fever, the considerable variation in blood levels from patient to patient with comparable dosage is not altogether surprising. Flinn et al.[6] have suggested that by limiting the fluid intake one can decrease the rapid urinary excretion of PABA and thus maintain higher blood levels with smaller doses. We would favor a therapeutic increase in the dose rather than limit the intake of fluids especially in view of the relatively non-toxic character of PABA.

On the average, a dose of 0.4 gm. per pound per day in our series of 15 cases in children yielded a level of approximately 30 mgm. %. This is probably in the range of an adequate blood concentration. There is insufficient clinical evidence as yet to indicate that blood levels higher than 30–40 mgm. % offer any singular advantage in spotted fever.

It is to be noted that 24 to 48 hours was often required to attain adequate concentrations after the initiation of PABA therapy.

In this series, PABA blood levels were obtained daily about one hour after the previously administered dose. Experimentally, it would be desirable to obtain PABA levels at frequent intervals during the day with due regard for intake and output of fluids and the renal status. One PABA blood assay per day, however, ordinarily suffices for clinical purposes.

CLINICAL MANIFESTATIONS OF TOXICITY

There have been few reports of untoward clinical effects in the use of PABA. Woodward[8] found that an occasional child became delirious and irrational when the PABA lood level exceeded 60 mgm. %; these symptoms promptly disappeared when the blood level was lowered. Two patients of this series (#5 and #6) became delirious and comatose at a time when the PABA blood levels ranged between 40 to 80 mgm. %. However, both of these children were severely ill with a complicating parotitis and bronchopneumonia. It was difficult to determine whether the disorientation and lethargy noted in these two patients was due to the disease per se or to the toxic effects of the drug. In an attempt to dissociate the effects of the drug from the disease, a series of six control children, selected at random, were given therapeutic doses of PABA for four consecutive days. In spite of the high drug levels (up to 54 mgm. %) attained, no evidence of drowsiness or lethargy was observed, suggesting that the apathy and disorientation in our cases #5 and #6 may have been due to the disease rather than to the drug.

EFFECTS OF PABA ON BLOOD CHEMISTRIES

In 10 patients in this series, a total of 26 NPN determinations were done. Of these, 19 or 73% were below 35 mgm. % while in 7 instances (27%), the NPN was above 35 mgm. %. Six of these latter seven determinations ranged between 40 to 53 mgm. %. In the seventh instance, the NPN rose to 90 mgm. % while concomitantly the PABA blood level was 40 mgm. %. PABA was promptly discontinued and the NPN dropped to 26 mgm. % 48 hours later. In all cases, a good urinary output was maintained with no especial attempt being made to alkalinize the urine. An elevated NPN does not necessarily constitute a contraindication to the use of PABA or its continuation, unless the nitrogen retention goes inordinately high. The slightly elevated NPN noted in about one-fourth of the cases in this series is probably attributable to a lowered blood volume resulting from extravasation of fluids and plasma proteins into tissue spaces through damaged blood vessels. This results in a lowered blood pressure and glomerular filtration pressure with a resulting pre-renal azotemia. It is of importance therefore to perform periodic NPN determinations to ascertain the extent of renal function so that a rapid rise in PABA blood levels may be anticipated. There is no evidence at this time that PABA produces kidney complications in spite of its chemical similarity to the sulfonamide drugs. Of 79 urines examined in this series, there was no evidence of hematuria or crystalluria, though many of the urines had an acid reaction.

Pathologically, it has been found that the liver shares similar generalized capillary damage noted in most other organs in Rocky Mountain spotted fever. There is both edema throughout the lobule and a localization of capillaritis in the periphery of the lobule. One would expect therefore some clinical pathological indices to reflect this liver dysfunction and such was found to be the case. A total of 34 cephalin flocculation tests were performed in 14 patients in this PABA treated series. Of this number, 24 determinations ranged between 3+ to 4+ (71%) while 6 (18%) of the cephalin flocculations were 2+ and 3 (9%) were 1+. Only one cephalin flocculation test out of 34 was negative and in this instance, it was on the second day of illness. Otherwise there was no positive correlation between the day of the disease and the extent of positivity of the cephalin flocculation test. In some of the patients the cephalin flocculation was still 3+ to 4+ for 20 to 30 days after the onset of the disease. Follow-up tests beyond 4 weeks to determine the duration of this index of liver dysfunction were not done. Clinically the liver was only infrequently enlarged and there was no evidence of jaundice in any case.

In a previous report [10] we discussed the ability of PABA per se to produce an increase in cephalin flocculation positivity. A series of six normal controls ranging in age from 3 to 11 years were given 0.33 gm. of PABA per

pound of body weight in 24 hours for 4 consecutive days and daily cephalin flocculation tests were obtained. In all four cases, the titer rose to 3+ to 4+ within 24 to 48 hours after the initiation of PABA. Thus there is some question whether the marked cephalin positivity noted in the spotted fever cases represents an effect produced by the disease or the drug or both. It is worthy of note that three out of seven cephalin flocculation tests obtained prior to initiation of PABA in the treated cases of Rocky Mountain spotted fever ranged from 3+ to 4+ indicating a production of liver dysfunction by the disease itself. In the majority of instances the cephalin flocculation test remained positive for a considerable period after PABA was discontinued.

One can probably conclude that both Rocky Mountain spotted fever and PABA are capable of producing an increase in cephalin flocculation positivity. The pathological effect on the liver by the disease could adequately explain this phenomenon in the cases of Rocky Mountain spotted fever; however, the apparent propensity for increase in cephalin positivity by PABA is not so clear nor can its clinical significance be interpreted at the present time. In three PABA treated cases who died of Typhus fever, Snyder et al.[13] reported that no lesions were seen in the liver which could be ascribed to poisoning by PABA.

THE PRESENCE OF A REDUCING SUBSTANCE IN THE URINE DURING PABA THERAPY

In the present series, it was noted that frequently while on PABA therapy a reducing substance was found in the urine producing a green or yellow reduction with Benedicts copper reagent.* Initially this was regarded as

* It has long been known that certain aromatic acids such as benzoic and phenylacetic acid may be conjugated with glucuronic acid in the animal organism. Hanson et al.[14] reported that the average daily excretion of glucuronic acid by normal rabbits was 140–150 mgm. Dziewiatkowski and Lewis[15] have postulated that when a significantly increased content of glucuronic acid is observed in urines after the administration of compounds which are known to conjugate with it, these values represent increases in true glucuronic acid and the calculated extra glucuronic acid gives an accurate measure of the amount of foreign compound thus conjugated. Urines containing extra glucuronic acid all reduced Benedict's reagent for sugars.

The ease with which the urines reduced Benedict's reagent without previous hydrolysis suggested that we were concerned with a labile glucuronide such as a benzoylglucuronide resulting from the conjugation of PABA with glucuronic acid. It is planned to test for glucuronic acid in future cases with the Jaffe test (picric acid and sodium hydroxide) and the Tollens test (napthoresorcinol). More recently a test for the presence of glucuronic acid has been described by Dische[16] in which concentrated sulfuric acid is mixed with the test solution followed by the addition of carbazole; this results in the appearance of a pink color within a few minutes and is considered to be more specific reaction than either the Tollens or Jaffe test.

an adventitious finding; however, its frequency in our first few cases prompted a more careful determination of the etiological factor involved and in the later cases in the series, urines were obtained regularly both before, during, and after termination of PABA therapy.

In 13 of our cases, a total of 79 urinalyses were performed. Of these, nine urines in different patients were examined prior to PABA administration and none showed any evidence of a reducing substance. Forty-three urinalyses performed during PABA therapy, however, showed a reducing substance in 24 instances (55%); there was no associated diacetic acid or acetone and there had been no concurrent administration of intravenous glucose in any of the patients. A total of 27 urinalyses were done following termination of therapy; four of these showed a reducing substance only during the first 24 hours after PABA had been discontinued. All subsequent urines were entirely negative. The presence of this reducing substance in the urine was not correlated with the PABA blood level nor with the duration of therapy. It usually appeared within 12 to 24 hours after initiation of PABA therapy and disappeared within a similar interval after the drug was discontinued. In the majority of instances, the reduction was only 1+; however, an occasional 2+ to 3+ reduction was noted. In one patient, six out of eight urines examined while on PABA therapy showed this reducing reaction. Only 2 patients out of 13 whose urines were examined repeatedly during therapy showed no reducing substance.

EFFECT OF PABA ON THE WHITE CELL COUNT

One of the few untoward effects noted with PABA administration has been the production of a leukopenia. This has been noted in several reports. The instances of its occurrence are comparatively few and there has been no report of agranulocytosis in any case. It is mandatory, however, to do frequent white blood counts during the course of therapy. In this series, a total of 125 hemograms were performed, an average of eight per patient. In eight of the seventeen cases treated with PABA, the count dropped below 5000 during the course of therapy; there was no associated granulocytopenia. The decrease in the white cell count was for the most part gradual and usually occurred between the fourth and sixth day. Following termination of the drug, the white cell count rose promptly to its normal level within 24 to 72 hours. We do not believe that premature discontinuation of PABA therapy is indicated unless the white count goes below 3000.

That the overall white cell count is decreased during the course of PABA therapy in the majority of instances even though a definite leukopenia does not always appear, is suggested statistically by a comparison of hemograms in PABA treated cases in this series with those obtained in the series re-

ported by Peterson et al.[12] where PABA was not used (Chart 6). In an untreated group of 26 cases, Peterson and his associates performed 70 white and differential cell counts, and found a relative leukopenia during the first five days varying from 4000 to 10,000. During the second week there was a definite leukocytosis ranging from 13,700 to 17,800. In our series of 17 cases, a total of 125 white and differential cell counts were performed. We similarly noted a relative leukopenia during the first 5

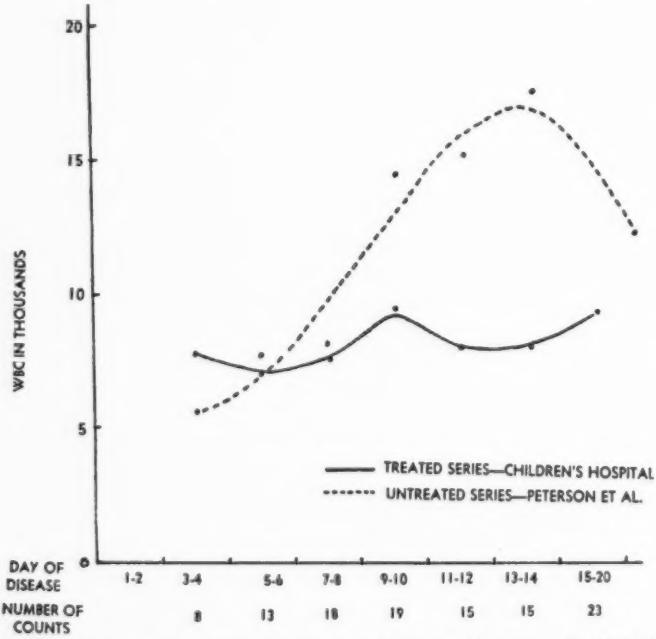

CHART 6. A comparison between the average white cell counts obtained during the course of spotted fever in treated and untreated cases.

days averaging 6700 to 7500. During the second week where one would ordinarily expect a definite leukocytosis in untreated cases, we found the white cell count usually ranging between 7200 to 9200. Thus on the average, a relative leukopenia was noted throughout the entire course of the disease in PABA treated cases. A leukocytosis above 12,000–15,000 was noted in only 3 of the 17 cases in our series, and in all three instances, the patients were acutely ill with associated bronchopneumonia and/or myocarditis. This leukocytosis may be of some value in PABA treated patients of Rocky Mountain spotted fever as an index of a complicating infection.

CONCLUSIONS

1. PABA was used in 17 cases of Rocky Mountain spotted fever during the summers of 1946 and 1947 with recovery of all patients. Both the morbidity and degree of toxicity was decreased.

2. The earlier the initiation of PABA therapy, the better the response. Favorable therapeutic results can probably be expected if the drug is started before the seventh day. The optimal time for initiating treatment probably lies between two to four days after the onset of the disease. The importance of early diagnosis is emphasized.

3. There is considerable variation in the PABA blood level achieved with comparable dosage, there being no definite linear or curvilinear correlation between dosage and blood concentration. On the average, a dose of 0.4 gm. per pound in 24 hours in a 2 hour divided dosage schedule was found to be satisfactory in children.

4. PABA has few toxic manifestations. A leukopenia without granulocytopenia was found to occur in some cases. Cephalin flocculation showed an increase in positivity during PABA therapy.

5. A reducing substance which produced a green or yellow reduction with Benedicts reagent was found in 55% of the urines examined during PABA therapy. This reducing substance is probably a benzoylglucuronide resulting from the conjugation of PABA with glucuronic acid.

We wish to express our sincere appreciation to Dr. E. Clarence Rice for his invaluable assistance with the laboratory procedures.

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PRECOCIOUS AND OTHER ABNORMAL PHASES OF SEXUAL DEVELOPMENT IN INFANTS AND CHILDREN

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Precocious and other abnormal phases of sexual development are conditions not frequently encountered in the routine practice of pediatrics; however, because of the difficulty in establishing definite etiological diagnoses in such conditions it was deemed of importance to present this paper.

The infant or child with bizarre and dramatic symptoms of precocious sexual development often poses an interesting and difficult diagnostic and therapeutic problem.

DEFINITIONS

Because there is considerable confusion in nomenclature concerning precocious sexual development, the following definitions of terms are set forth:

1. *Puberty* is achieved when the ability to procreate becomes established. It is manifested by the first ovulatory menstrual cycle in the female and by the appearance of mature semen in the male. Puberty occurs approximately midway during the period of adolescence.
2. *Sex Precocity* (Macrogenitosoma praecox) is characterized by genital development which approaches adult proportions during the first eight to twelve years of life.
3. *Adolescence* is the period which commences when the sex characteristics first begin to develop and ends when the individual reaches full sexual maturity.
4. *Precocious puberty* (pubertas praecox) is characterized by the ability to procreate during childhood. There are two types:
   a. *Pubertas praecox virilis* ("infant Hercules")—this is Reismar's muscular type.
   b. *Macrosomia congenitalis adiposa*—this is Christinsen's obese type.
5. *Virilism* in the female is characterized by masculine over-development.

PHYSIOLOGY

Fuller Albright emphasizes that endocrinologic diseases are generalized diseases. In this light it is not advisable to delimit the signs and symptoms of precocious sexual development to just the primary and secondary sex organs for the entire individual is affected. The normal endocrine balance is maintained by the overall action of the master gland, the pituitary. Any

endocrine organ, however, which is acted upon in any way (such as by tumors, artificial hormones, etc.) in turn acts on the rest of the endocrine system. There is, therefore, a close interrelation of the endocrine glands. As a rule, precocity is usually the result of definite endocrinologic disease although other factors apparently non-endocrine in type are known to be of less frequent etiological importance. For example, disorders of the central nervous system may rarely be associated with pubertas praecox. The mechanism of production of this form of premature development remains obscure.

In the normal preadolescent child the gonads are relatively quiescent. Shortly before the first external manifestation of adolescence becomes evident the pituitary stimulates the gonads and the adrenal cortex to increased activity producing testicular or ovarian and adreno-cortical hormones which determine the extent of development of the accessory sex organs. Some investigators believe that puberty is affected in a chronological order by the following organs: thymus, pituitary, thyroid, parathyroid, adrenal, anterior pituitary and ovaries and testes.

DIAGNOSIS OF PRECOCIOUS VERSUS NORMAL SEXUAL DEVELOPMENT

In those children who reach full sexual maturity early or develop genitally prematurely there is a general somatic overgrowth in which all tissues and organs are involved, such as increased stature, early mature bony and muscular development, and early epiphyseal ossification. Often there is an adult thought and speech context. On the other hand, it has been stated by some observers that a coordinate deviation in the curve of mental growth does *not* occur. In the male the voice usually deepens and often there is an adult sexual philosophy concerning the opposite sex as well as a general adult philosophy. The penis enlarges, pubic and facial hair appears and the testes are usually of normal size—spermatogenesis being absent. The female exhibits premature physical and gonadal development; the breasts become enlarged, the labia and clitoris hypertrophied and hair appears prematurely on the mons veneris, face and axillae. Menstruation and enlargement of the ovaries and uterus may occur. Rapidly the sexual organs enlarge, secondary sexual characteristics become pronounced, and full sexual maturity is established. When virilism occurs in the female it is usually preceded by pseudoprecocity.

Adolescence usually occurs in girls between the eighth and thirteenth years and in boys between the ninth and fourteenth. Puberty is generally reached between the ages of ten and sixteen and one-half years in the females and between eleven and seventeen and one-half years in the male. In the Orient menstruation begins early, often at nine or ten years of age, and in the

temperate zones it usually occurs between the ages of twelve and fifteen years.

The incidence of extremely precocious puberty is considerably rarer among boys than among girls. A child is definitely precocious sexually if maturity has occurred by the ninth year and if cyclic menstruation begins before the tenth year.

ETIOLOGY

In general there are three main causes of precocious and other abnormal phases of sexual development in infants and children. They are as follows:

I. Hyperplasia or neoplasia of ovarian, testicular, or adrenal-cortical cells.

II. Tumors and other disorders involving the central nervous system.

III. Other rare or controversial disorders such as physiologic early puberty, Albright's syndrome, therapeutic or experimental administration of hormones, and disturbances of the thymus gland.

A discussion of the etiological factors responsible for abnormal sexual development in infants and children follows.

ADRENAL CORTEX

Aberrations of the adrenal cortex most commonly produce early or pronounced masculinization (adrenal dwarf, "Cushing's") of the male, and precocious feminization or masculinization (pseudo-hermaphrodite fetus, "Cushing's") of the female; however, feminization of the male has been known to occur. Adrenal cortical neoplasms although rare are the most frequent cause of precocity in the male, less frequent causes being benign hypertrophy and hyperplasia of the adrenal cortex. More rarely the etiological factor may be a supernumerary adrenal in the broad ligament. The most logical theory of the etiology of this syndrome was discussed by Bulloch and Sequeira in 1905 and by Dwynn in 1912. It was their belief that the effect is due to an acceleration of the normal physiological function of the adrenal cortex. The adrenal cortex elaborates hormonal substances of two distinct general classes, the first class having its effect on the metabolism of salt and water, electrolyte balance, regulation of carbohydrates, and other less important systems and the second class exhibiting the action of the male or female hormones. The sex hormones are believed to be secreted by the zona reticulosa of the adrenal cortex and if these hormones are active during early infancy, precocious sexual development results.

Rarely Cushing's syndrome may occur. In this disease the outstanding

finding is obesity while the signs and symptoms of sexual precocity are often minimal.

The diagnosis of an abnormality of the adrenal cortex is usually aided by finding a unilateral abdominal mass, an increase in urinary ketosteroids (end product of androgenic activity), and possibly by pyelographic studies.

THE GONADS

The gonads are stimulated by the anterior pituitary, that stimulation becoming manifest normally at puberty. Prior to puberty both sexes secrete about equal amounts of androgens and estrogens under normal circumstances. Because of the under-development of the gonads this suggests that the adrenal cortex possibly is the source of these hormones rather than the gonads themselves. At puberty, however, the greater output of male or female hormones parallels the development of the testes or ovaries.

OVARIAN TUMORS

The most common cause of precocious sexual development in the female is the granulosa cell tumor of the ovary, a less frequent cause being a theca cell tumor. Approximately one-third of the cases of granulosa cell tumor reported in the literature occurred in the preadolescent age group. This tumor secretes estrogen with the resultant development of a picture of true pubertas praecox. Granulosa or theca cell tumors are thought to be derived from an arrested growth (in embryonic stage) of mesenchymal cells that are predisposed to becoming feminine. These tumors are usually malignant. Rarely, such tumors as follicular cysts and thecomas are associated with sexual precocity. Cyclic menstruation has been reported to begin as early as four months of age in association with the above tumors. Arrhenoblastomas are masculinizing ovarian tumors and are rarely seen in children.

A unilaterally enlarged ovary often aids in the diagnosis as does a marked elevation in the urinary estrogen content.

TESTICULAR TUMORS

Neoplasms affecting the male gonads are very rare and perhaps due to their rarity are usually subject to a great deal of controversy regarding their pathological characteristics and diagnoses. The testicular interstitial cells of Leydig produce the male hormone testosterone which is mainly responsible for secondary male characteristics. Tumors of the interstitial cells of Leydig are the most frequent testicular causes of precocious puberty in the male. Rare cases of feminization of the male due to teratomas of the testicles have been reported.

Table Listing Various Etiological Conditions Responsible for Abnormal Phases of Sexual Development in Infants and Children and the Usual Clinical Findings Encountered in Each Condition

GLAND OR ORGAN INVOLVED	DISEASE PROCESSES	FEMALE		MALE	
		Feminization (Precocious puberty)	Masculinization	Feminization	Masculinization (Precocious puberty)
Adrenal (cortex)	Neoplasms (a) Benign (b) Malignant Benign hypertrophy; Benign hyperplasia; Supernumerary adrenal in broad ligament; Cushing's syndrome	++	+ (fetus pseudohermaphrodite, Cushing's etc.)	+ (rare)	+++ (adrenal dwarf "Cushing's," etc.)
Ovary	Neoplasms (a) Benign (b) Malignant Cysts	++ (granulosa cell tumor; theca cell tumor; follicular cysts; thecomas)	+ Extremely rare (arrhenoblastomas)		
Testicle	Neoplasms			+ (rare Teratoma)	+ (Interstitial tumor of Leydig)
Hypothalamus	Neoplasms; Hypofunction; Atrophy; Chronic internal hydrocephalus with atrophy of:	+	+ (rare)		+
Floor of 3rd Ventricle	Hamartomas, etc.				
Pituitary (anterior)	Basophilic adenoma; Pituitary basophilism; Cushing's	+ (rare)	+	+	+ (rare)
	Acidophilic and Chromophobic adenoma		+	+	
Pineal Body	Pinealoma				+ (?)
Brain (not localized)	Inflammatory processes; Mongoloid idiocy	+			+
Other	Physiological early puberty; Functional hypergonadism; Constitutional disorders; Albright's syndrome; Therapeutic administration of hormones; Experimental administration of hormones; Thymoma	+			+

In cases of precocious puberty due to tumors of the interstitial cells of Leydig the Ascheim-Zondek test may be positive and elevated prolan urinary levels are present.

TUMORS AND OTHER DISORDERS INVOLVING THE CENTRAL NERVOUS SYSTEM

The most important disorder falling under this classification is the condition in which there is a lesion involving the floor of the third ventricle or the hypothalamus. It is controversial whether a tumor confined to the pineal gland alone has ever caused precocious sexual development, most authors believing that the etiology of the precocity is a disorder of the region surrounding the pineal body or a pinealoma producing pressure on the hypothalamic region.

The lesions of the central nervous system causing pubertas praecox or other abnormal phases of sexual development in infants and children are as follows:

1. *Pineal Body Tumor.* Pinealomas producing sexual precocity in the male have been reported; however, these are debatable as mentioned previously. There is no mention in the literature of pineal body tumors producing sexual precocity in the female.

2. *Tumors of the Pituitary (Anterior).* Basophilic adenomas of the pituitary often cause pituitary basophilism or Cushing's syndrome. This may be manifested by sexual precocity early in the course of the disease; however, it more frequently is associated with masculinization of the female or feminization of the male. Acidophilic and chromophobe adenomas of the pituitary may also produce masculinization of the female or feminization of the male.

3. *Tumors of the Hypothalamus—hypofunction and atrophy of hypothalamus—tumors (hamartomas, etc.) of floor of third ventricle involving tuber cinereum and mammillary bodies—chronic internal hydrocephalus with resultant atrophy of hypothalamus.* These are infrequently found to cause precocious puberty as well as masculinization of the female.

4. *Inflammatory Processes Involving the Brain.* Syphilis, tuberculosis, epidemic encephalitis, measles encephalitis and malaria may be etiological in producing precocious puberty.

6. *Mongoloid Idiocy.* A case of pubertas praecox was reported by Schlockter and Cotte in a Mongoloid idiot of eleven years. Tumors were adequately excluded as the cause.

Aids in the diagnosis of lesions of the central nervous system associated with abnormal sexual development in infants and children are as follows: Increased intracranial pressure, history of neural infections and inflammations, lower urinary hormonal excretion, occasional obesity, emotional disturbances and physical signs of neurological localization.

OTHER CONTROVERSIAL OR RARER DISORDERS

Opinions vary widely about the etiology of precocious sexual development and the expressed causes are manifold.

1. *Physiological Early Puberty (Functional Hypergonadism).* Novak has reported nine cases of early cyclic menstruation in the female due to what he terms "constitutional disorders." Schauffler feels very strongly that if these nine cases were reviewed a familial history could be obtained in at least a few. Cases of physiological early puberty are extremely rare and therefore it is especially wise to be suspicious of pathology in all patients with symptoms of early maturation.

Due caution should be taken that no possibility is overlooked in the attempt to diagnose the disorder. Furthermore the patient should be followed subsequently for signs of enlarging tumor masses. The number of emissions and erections are important guides in the male, while in the female increased libido and early menstruation are important. Studies of the hormonal excretion of these patients may also prove to be of great value.

The management of these cases is often very difficult. Schauffler warns that endocrine therapy should be avoided as much as possible. It must, nevertheless, be remembered that hormonal therapy may prevent dwarfism which is a fairly common finding in those patients who attain adulthood. Possibly temporary sterilization may be indicated in the female. If not, constant vigilance must be maintained to prevent early bisexual activities.

2. *Albright's Syndrome (Osteitis Fibrosa).* This syndrome is characterized by precocious puberty, fibrocystic bone disease, and pigmentation of the skin. The osseous lesions tend to be unilateral. The disease has been known to exist for eleven years with little evidence of deterioration. There is no known therapy and the prognosis is uncertain.

3. *Therapeutic Administration of Hormones.* The use of hormones in young children often has a marked effect on sexual maturation. The end result of this may be dwarfism. Far more important are the psychological problems arising from the early maturation. For these reasons care should be taken that hormonal therapy is not misused in children. The indiscriminate use of chorionic-gonadotropin in failure of descent of the testicles is to be condemned. The use of estrogens in vaginitis (especially gonorrheal is not recommended.

4. *Experimental.* A great deal of experimentation has been accomplished in this field and nearly all of the endocrines as well as the thymus have been accused of causing precocious sexual development.

As paper bursts rapidly into flames and burns itself out quickly, those children who develop sexually at an extremely abnormal early age never become, without adequate treatment, normal adults. Their adult appearance is reached earlier but, if they survive, they are never as fully

matured as normal individuals and in some instances remain rather dwarfish in appearance.

It is plain, therefore, that precocious and other abnormal phases of sexual development in infants and children represent a challenge for proper diagnosis and early treatment. Those patients who live to adulthood may possibly be helped by adequate management, but the abnormal physical changes which have already occurred can never be completely retracted. If precocious or other abnormal phases of sexual development are recognized early and immediate treatment undertaken when indicated, the gratification of performing startling improvement may be immeasurable.

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ALKALOSIS WITH OBSTRUCTIVE VOMITING

Case Report No. 134

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The pediatrician is often called upon to handle deficiencies in the electrolyte equilibrium of the extracellular fluids of infants. In recent years, the bulk of the literature on this subject has concerned itself with conditions associated with diarrhea, loss of fixed base, and acidosis. It is therefore deemed appropriate to report a case of the opposite extreme, alkalosis from anion loss, and discuss the physiologic mechanisms involved.

REPORT OF CASE

R. B., a 39 day old negro boy, was admitted to the hospital because of vomiting for one month.

He was born at term, at home, unattended, and taken to a local hospital post-partum. The birth weight was 5 pounds, 12 ounces (2,614 gm.). He was breast fed for four days in the hospital, but at home was given evaporated milk feedings. Vomiting began on the sixth day of life and soon became regular, projectile, and occurred shortly after feedings. The vomitus was never colored. During the two weeks before admission the stools were scanty, thin, greenish-brown. No previous medical care had been sought during the month long illness.

The family history was non-contributory.

Physical examination revealed a thin, marasmic infant, weighing 5 pounds, 3 ounces (2,360 gm.). Respirations were slow, shallow, and at times almost imperceptible. The cry was weak and faint and the infant's activity was poor. There was no subcutaneous fat, and almost no skin turgor. The mucous membranes were dehydrated. There was upper abdominal distention, especially on the left, and large, clearly visible peristaltic waves originating in the left upper quadrant and progressing downward and to the right, disappearing just beyond the umbilicus. A firm, movable mass about 2 cm. in diameter was palpable deep in the upper epigastrium near the right costal margin.

The laboratory studies are summarized in Table 1 and discussed below.

When the severity of the alkalosis became apparent, a continuous intravenous infusion was initiated and 5% glucose in normal saline given. Two grams of ammonium chloride was given twice by rectal drip, about half being retained each time. Blood and plasma were added to the intravenous infusion daily. Improvement was rapid. A Rammstedt pyloroplasty was performed on the third day.

The post-operative course was uncomplicated. On gradually increased feedings, weight gain began on the fourth post-operative day. The patient weighed 6 pounds, 8 ounces (2,950 gm.) at the time of discharge on the 24th hospital day.

DISCUSSION

Table 1 and Figure 1 depict the situation of this infant in respect to electrolyte balance. As illustrated in Figure 1 (*B*) there was an electrolyte deficit of about 53 meq./liter each of anion and cation at the time of admission. The chloride loss of 71.5 meq./liter had been partially compensated by the increase in the HCO_3 compartment and concomitant excretion of fixed base as the bicarbonate salt, through the mediation of renal

TABLE 1

	HOSPITAL DAY											
	A	1	2	3	4	5	6	7	8	9	10	11
CO_2 Combining Power (Vol. %)	102	96	67	64								
Blood Sodium Chloride (mg./100 cc.)		181	231	495				450				
NPN (mg./100 cc.)		75										
Urine Reaction		alk.			alk.	alk.		alk.	neutral	alk.	alk.	acid

regulatory mechanisms. For this reason, the urine was highly alkaline. Thirty-six hours later (1, *C*) following infusions of sodium chloride and administration of ammonium chloride by rectum, there had been some slight further loss of plasma equivalence, but restoration of the chloride component had begun. The alkaline urine is evidence of the continued loss of base.

Figure 1, *D* shows the picture 72 hours after admission, the day of operation. Despite the alkaline urine, there was at that time almost complete restoration of plasma electrolyte. It will be noted from Table 1 that complete compensation did not occur until the 11th day in the hospital, eight days after operation, when along with weight gain and adequate enteral fluid intake the urine finally became acid.

Alkalosis to this degree is no longer a frequent finding in patients with pyloric stenosis, since they are being recognized early and usually given the benefit of early surgical therapy combined with electrolyte replacement.

Although sodium chloride solution given parenterally will eventually

correct alkalosis through the selective renal regulatory mechanism, it is probably advantageous to use more direct means in the severe cases.

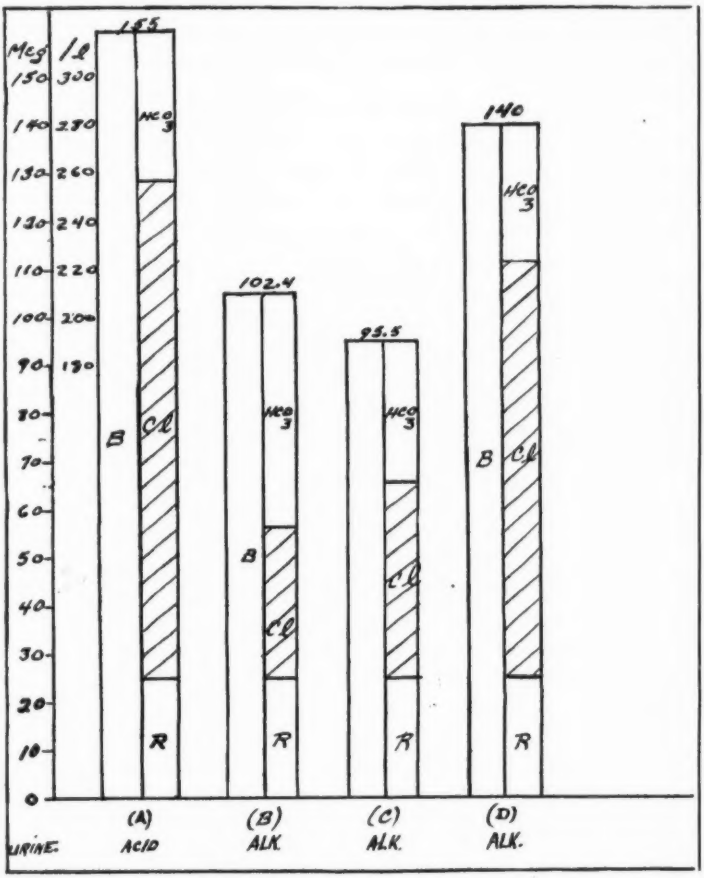

FIG. 1. Plasma electrolyte values expressed in Milli-equivalents per liter (after Hartmann). (*A*) Normal values; urine is acid. (*B*) Patient R. B., on admission: chloride depletion with compensatory loss of base, increase in bicarbonate and alkaline urine. (*C*) Second hospital day: chloride replacement beginning. (*D*) Third hospital day: almost complete restoration of chloride and base. Pyloroplasty performed at this stage. ("*R*" represents unmeasured anion, such as protein, sulphate, and phosphate, assumed to remain unchanged.)

Hartmann [1] has reported the use of dilute hydrochloric acid intravenously. A somewhat less hazardous method, employing $\frac{1}{6}$ normal ammonium chlo-

ride solution was reported originally by Forbes and Erganian.[2] Their studies showed a drop of 0.88 to 1.77 volumes % of carbon dioxide combining power for each 1.0 cc. per kilogram of body weight of the solution administered parenterally. This method was also used successfully in a case reported recently by Wooley et al.[3], at the Children's Hospital of Michigan.

Our attempt at administration of ammonium chloride by rectum must be considered unsuccessful since the fall in carbon dioxide combining power in our case was no more rapid than in those cited by Hartmann[1] treated with saline and Ringer's solutions.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
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By Invitation: Phillip Litvin, M.D.

Harold W. Bischoff, M.D.

This six year old colored female entered Children's Hospital on June 28th with a chief complaint of having vomited every morning for three weeks prior to her hospital entry. For the same duration of time the child's mother noticed that the patient's behavior began to change. She appeared to be emotionally unstable and would often cry spontaneously. The mother noticed that the child's gait was unsteady and that she could not walk in a straight line. The eyes would cross frequently; however, they always would come back to a normal position. For a few nights before her admission the child had been awakening from sleep screaming because of nightmares and she had fallen out of bed almost every night. Blinking occurred infrequently. There was no complaint of headache or other pain. The birth, past and family histories were non-contributory.

Physical examination revealed a well developed and nourished colored female of stated age (6 years) who did not appear to be in any distress. It was noted that she stared constantly. Examination of the thorax and abdomen revealed nothing remarkable. Blinking of the eyelids occurred about once a minute. The sclerae were clear. The reactions to light and accommodation were not tested because of the administration of a mydriatic. Fundoscopic examination revealed about 1 to 2 diopters of papilloedema of the right eye and a suggestive papilloedema of the left disc. Examination of the ears, nose and throat was negative.

Neurological examination showed the following:

Cranial nerves:

I Negative
II Continuous staring expression
III Negative
IV Negative
V Motor—negative
Sensory—corneal reflex on right practically obliterated, on left weak
VI Right lateral rectus non-functioning
VII There appeared to be some right sided weakness
VIII Auditory—grossly negative
Vestibular—grossly negative

IX Negative
X Negative—heart rate normal—B.P. 105/50
XI Negative
XII Slight deviation of tongue to right on protrusion.

Gait. The child walked with a shuffling gait and appeared to be "unsteady." There was some over-adduction of the left foot when walking.

Romberg test—positive to the right.

Deep reflexes—physiological.

Babinski—positive bilaterally.

Sensory—no sensory changes noted over body.

On the day of hospital entry a spinal tap was performed. The cerebrospinal fluid emerged under no increase in pressure, and it was clear and colorless. Laboratory examination of the fluid revealed 5 mgm. % of protein, a normal reduction of sugar, and less than 1 cell per cu. mm. A spinal fluid Wassermann was negative, and a colloidal gold curve was normal.

Roentgen examination of the skull in the P.A. and lateral positions the day after hospital entry revealed no evidence of fracture or any other osteal or pathologic change. The sella turcica was normal. There was no other evidence of abnormality.

A tuberculin test performed with 0.1 mgm. O.T. was negative. The hemogram and urinalysis on entry were both within normal limits.

Two weeks after entry the child was taken to surgery and the right lateral ventricle entered through a posterior approach. An internal hydrocephalus was found. A right sub-occipital craniectomy was carried out. Because of the patient's condition the wound was closed without finishing what was originally contemplated.

Four days later operation was again scheduled but cancelled because of inability to induce proper anaesthesia. Seventeen days later the patient was again taken to the operating room with the intent of performing a sub-occipital craniotomy. The child again became cyanotic whenever she was put in position for operation and again the operation was cancelled.

During the time of her hospital stay the child gradually became more and more lethargic. Twelve days after craniotomy fundoscopic examination was essentially negative. The patient was unable to move her eyes to the right or left but was able to move them vertically.

There was a gradual weight loss recorded up until two months before her demise when she was considered too ill to disturb.

The child died approximately five months after her hospital entry. There was an agonal temperature rise to 106.8 F.

DISCUSSION

Philip Litvin, M.D.: The case in question represents the typical findings which involve the differential diagnosis of brain tumor. As in most of these

cases the early symptoms are usually mild and the patients are treated for a multitude of diseases. Here we have the six year old child who is restless and vomits for a period of three weeks. Vomiting over a prolonged period of time is always indicative of cerebral or cerebellar irritation. Psychogenic vomiting in a six year old, while it occurs, is so rare it can be discounted particularly in this case where there are definite findings pointing to intracranial involvement. The symptoms have to be considered as facets of one picture. The disease that explains them all is the most likely and I am sure the offending cause in this case. In addition to the vomiting there was definite evidence of increased intracranial pressure as evidenced by the papilledema bilaterally but more so on the right. The fixed stare that is described in conjunction with later inability to use the right lateral rectus muscle point to a sixth nerve involvement.

Unfortunately the description of the tongue involvement is given as slight deviation to the right on protrusion. No description is offered of any fibrillary twitchings. The only other findings are those of a positive Romberg to the right, ataxia of gait and bilateral Babinski. There is also a notation of absent right corneal reflex.

Before we even discuss the spinal fluid findings we should try to visualize and summarize the findings. A definite sixth nerve on the right, a third on the right, seventh on the right and twelfth on the right, with pyramidal signs bilaterally, namely a bilateral Babinski. In order to catch all these nerve fibers the most likely place is the pons.

Now let us consider the spinal fluid dynamics. Unfortunately the pressure was not recorded. It is almost impossible to determine pressure by the use of visual estimation of the drops. The variation is so great with each individual that it is almost worthless. Pressure should be measured by a water manometer. If it is worthwhile studying the fluid then it is worthwhile doing the dynamics. In the presence of papillodema, it is not considered good practice to do an air study through the spinal route. The review of the x-rays in this case shows no increased intracranial pressure. The sella is not abnormal and there is no erosion of the clinoids as you would expect in a pituitary tumor which expands. The plates show no erosion or enlargement of the foramen magnum. The notation is offered that after right ventricular tap a hydrocephalus was found.

The subsequent course in the hospital was down grade. It is not uncommon in pontine tumors for the respiratory center to be so labile and involved that proper anesthesia is hard to induce.

The most common types of tumor in the pons are (1) astrocytoma, (2) medulloblastoma and (3) hemangioma. The presence of hemangiomas in other parts of the body makes this type unlikely. They are usually found in the retina and skin. The progression in this case is that of a solid growing tumor, namely a definite space-displacing lesion or a space

occupying lesion. My diagnosis would be an astrocytoma of the pons (mid-line location) with degeneration or cyst formation in the tumor itself.

PATHOLOGICAL DISCUSSION

Fernando Leyva, M.D.: The convolutions of the brain were moderately flattened. Just superior to the left inferior olive in the pons there was a protruding mass of tissue which markedly compresses the inferior olive and pushes the medulla inferiorly and to the left. The external appearance was not much different from the rest of the positive tissue but the consistency was slightly firmer. Examination of the brain after formalin fixation revealed an oval shaped tumor mass which measured 6.0 x 5.5 x 4.0 cm. This was in the midline and occupied the usual position of the pons and cerebellar peduncles. The medulla appeared to be invaded by this neoplasm which did not appear to be well circumscribed. The tumor was bounded by the medulla, the fourth ventricle, the aqueduct of Sylvius and the third ventricle. The cerebellum was moderately compressed and the ventricular system was moderately dilated.

Microscopically the tumor was composed mainly of unipolar cells with dense broad long processes. However, occasional transitional astrocytes were present. There were no mitoses. Dr. Webb Haymaker, neuropathologist of the Army Institute of Pathology felt that this tumor represented a typical spongioblastoma polari and said that this type of tumor may be erroneously classified as being an astrocytoma because of the presence of astrocytes. However, this finding is only an incidental feature being merely a further stage in the evolution of the spongioblasts. Originally these cells are derivative of the primitive ependymal spongioblast. These tumors are usually of benign appearance; however, because of their location in the brain stem they are beyond surgical approach. According to Bailey, pontine tumors constitute approximately 15–20% of all intracranial neoplasms in children. Because of the absence of increased intracranial hypertension, they are difficult to diagnose accurately and many times they are not discovered until the time of autopsy. Histological classifications vary a great deal among neuropathologists. In a review of 13 cases cited by Bailey they are listed as follows; 3 glioblastoma multiforme, 3 spongioblastomas, 2 glioblastomas of low malignancy, 2 astrocytomas, 1 oligodendrogliomas and 1 mixed type.

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BIOGRAPHIES

Robert O. Warthen, M.D. (Precocious and Other Abnormal Phases of Sexual Development in Infants and Children, page 261), was born in Washinton, D. C. in 1921. He attended George Washington University, and received his M.D. degree from George Washington University School of Medicine in 1944. Following an internship at King's County Hospital in New York, Dr. Warthen entered the Navy, from which he was discharged in 1946. He completed a pathology fellowship in 1947, and joined the Children's Hospital resident staff in July of 1947. Several of Dr. Warthen's articles have been accepted by national journals, and are to be published soon. He is also a regular contributor to the Clinical Proceedings of Children's Hospital. He plans to practice Pediatrics on completion of his training.

Harold W. Bischoff, M.D. (Clinico-Pathological Conference, page 273), was born in San Francisco in 1908. He attended the University of San Francisco, and received his M.D. from the University of California in 1941. After an internship Dr. Bischoff entered the Navy, attending the Naval Medical School, and taking a very active part in Medical research. He has done part time practice in Pediatrics in San Francisco and in Carson City, Nevada. He has been a frequent contributor to the medical literature. After a year of Pediatric Pathology training here at Children's Hospital he joined the Pediatric Resident Staff in July 1948. His special interests include medical art and congenital heart disease.

Allan B. Coleman, M.D. (Alkalosis with Obstructive Vomiting, page 269), a native Washingtonian was born in 1921. He attended the George Washington University Junior College and Medical School and received his M.D. degree in 1943. He served his internship and Assistant Resident in Medicine at Gallinger Hospital from 1943 to 1945. Following which he went into the Army and was discharged in 1947. Dr. Coleman has been a resident at Children's Hospital during the last 18 months and has been a frequent contributor to the Clinical Proceedings. He plans to practice Pediatrics in the District of Columbia on completion of his training.